UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,562	12/05/2001	Daniel R. Salomon	080060-0002 (302018.3003-	2653

20572 7590 02/07/2006

GODFREY & KAHN S.C.
780 NORTH WATER STREET
MILWAUKEE, WI 53202

EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 02/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,562	SALOMON ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/27/05, 8/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/26/05 has been entered.

ACKNOWLEDGMENT OF AMENDMENT, REMARKS, IDS AND STATUS OF THE CLAIMS

2. The amendment, remarks and the information disclosure statement (IDS) and Form PTO-1449 filed 07/27/05 and 08/26/05 are acknowledged, entered and considered. In view of Applicant's request claims 1 and 13 have been amended. Claims 1-24 are now pending in the application. The rejection under 35 U.S.C. 103(a) over the prior art of record is maintained.

ARGUMENTS ARE NOT PERSUASIVE

CLAIMS REJECTION-35 U.S.C. § 103(a)

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Nawrocki et al (Transplantation Proceedings, Vol. 28, No. 6, pp. 3538-3539, 1996) taken with Cramer et al (Transplantation Proceedings, Vol. 29, page 616, 1997) and Schmid et al (Eur. Surg. Res., Vol. 30, pp-61-68, 1998) and further in view of Kouwenhoven et al (Transpl. Int., Vol. 13, No. 6, pp. 385-401, 2000)

Applicant's arguments filed 08/26/05 have been fully considered but they are not persuasive. It is noted that Applicant has amended independent claims 1 and 13 to recite "wherein the administration produces a decrease in cell-mediated immune responses including decreased circulating levels of CD8+ T cell in the peripheral circulation". Applicant's argument that the rejection under 35 U.S.C. 103(a) over the prior art of record is moot in view of the present amendment is unpersuasive. Contrary to Applicant's arguments, the decrease in cell-mediated immune responses including

decreased circulating levels of CD8+ T cell in the peripheral circulation would not change the outcome of the methods (i.e., methods of ameliorating and preventing chronic allograft rejections as claimed in claims 1 and 13, respectively). Further, with respect to the limitation of the effect of cellular immune responses, specifically decreasing the levels of circulatory CD8+ T cells as currently amended in claims 1 and 13; the reference of Kouwenhoven et al on page 391, right column teaches that the recognition of histoincompatible MHC alloantigens will provide an alloimmune response. In allorecognition, the MHC antigen is bound to the T cell receptor, wherein once the CD4+ T cell is activated, a cascade of events amplifies the alloimmune response which leads to clonal proliferation of alloreactive cells and stimulates CD8+ T cells to develop into mature cytotoxic effector cells which are cytotoxic to the graft cells. Therefore, in view of the above, one of ordinary skill in the art by administering compounds and/or agents that ameliorate and/or treat chronic allograft rejection would expect to produce a decrease in cell-mediated immune responses including decreased circulating levels of CD8+ T cells in the peripheral circulation.

Therefore, for the reasons discussed in the previous Office action and in view of the above, the combined teachings of the prior art makes obvious a method of ameliorating or preventing chronic allograft rejection by administering effective amount of cyclosporin in combination with 2-CDA and a pharmaceutical formulation for administration thereof including the limitations as currently amended in claims 1 and 13. Thus, it is made obvious by the combined teachings of the prior art since the instantly claimed invention which falls within the scope of the combined teachings of the prior art

method would have been *prima facie* obvious from said prior art disclosure to a person of ordinary skill in the art because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselete*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Best*, "the test of obviousness is not express suggestion of the claimed invention in any and all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them".

OBJECTION OF THE SPECIFICATION

4. The disclosure is objected to because of the following informalities: On page 5, line 18 in the recitation "a method or ameliorating....". It is believed to be typographical error. It is suggested to recite "a method of ameliorating.....". Also, on page 22, line 7 in the recitation "patents" instead of "patients". Appropriate correction is required.

CLAIMS REJECTION-35 U.S.C. 112 2nd PARAGRAPH

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in failing to recite where a decrease in cell-mediated immune responses including decreased circulating levels of CD8+ T cells occur. Also, claim 1 is

inconsistent with claim 13 and on page 6, second paragraph of Applicant's remarks filed 8/26/05 which states that a decrease in cell-mediated immune responses including decreased numbers of CD8+ T cells **in the peripheral circulation** (claim 1, currently **amended**). There is no such amendment in claim 1. Thus, amendment of claim 1 to be consistent with claim 13 and Applicant's remarks is suggested.

CLAIMS REJECTION-35 U.S.C. 112 1st PARAGRAPH

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13 –24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instantly claimed invention as amended in independent claim 13 is directed to a method of preventing chronic allograft rejection in an allograft recipient comprising administering to an allograft recipient a therapeutically effective amount of cyclosporine at least once weekly and a therapeutically effective amount of 2-chlorodeoxyadenosine at least once weekly, wherein the administration produces a decrease in cell-mediated immune responses including decreased levels of CD8+ T cells in the peripheral circulation.

However, the specification does not enable the method of **preventing** chronic allograft rejection as amended and claimed in the instant invention. The instant specification in Example 1 and Tables 1-5 demonstrates data regarding the number of T cells, and the CD4+ and CD8+ T cells subsets, in control rats and treated rats that had received a transplanted rat heart after 14 days and 90 days of treatment with various combinations of CSA and 2-CDA. The treatment regime produced a significant reduction at both 14 days and 90 days in number of lymph cells, number of CD4+ cells and number of CD8+ T cells as compared to the untreated control rats.

Thus, the invention is designed to provide treatment to allograft recipients with CSA in combination with 2-CDA, which showed a reduction in the incidence and severity of vascular intimal proliferation compared to animals receiving no treatment or animals treated with CSA alone. If the invention was to prevent chronic allograft rejection then the subjects of the treatment should have never manifested a decrease in cell-mediated immune responses including decreased levels of CD8+ T cells in the peripheral circulation. With regard to other aspect of this rejection, the prevention method involve administration of a various dosages and mode of administrations in the manner claimed. The specification on pages 6-10 provides protocols and/or information as to how the method of the invention can be used for the treatment and/or ameliorating chronic allograft rejections in animals. However, the specification does not provide any information or examples that would suggest the Applicant's invention could be used to prevent chronic allograft rejections. The specification is devoid of any working examples of the claimed pharmaceutical compounds to be administered for prevention

of chronic allograft rejections in the manner claimed. Further, on page 1, under Background of the Invention, in the instant specification, Applicant acknowledges by stating that a significant problem in organ transplantation today is the failure of current immunosuppressive strategies to significantly reduce the risk of rejection in kidney, heart, lung and pancreas transplantation more than one or two years post transplant. As a result, the tremendous gains made in the rates of one or two years survival of the transplanted organ over the last decade are largely lost at five years post transplant when the majority of transplant patients, especially those receiving cadaver donor organs, have lost function in the transplanted organ.

Furthermore, it is noted that Applicant stated on page 8, last paragraph of the remarks filed on 8/26/05 that in fact, review articles, written at the time of the invention was made to discuss the etiology and pathology of chronic graft rejection and emphasize: "there is still no treatment to **inhibit** or **prevent** (emphasis added) CTD (chronic transplant dysfunction), and a conclusive therapeutic strategy is not within hand's reach since its etiology and patho-physiology are poorly known". Thus, in view of the above there are no indicia that the present application enables the full scope in view of preventing and using the claimed agents as discussed in the stated rejection. The present application provides no indicia and no teachings/guidance as to how the full scope of the claims is enabled with regard to prevention.

Thus, the scope or prevention of the instantly claimed invention is speculative. Therefore, undue experimentation is necessary to determine if and under what conditions, the claimed invention as claimed is enabled, since a vast range of

pharmaceutical composition in all kinds of possible dosages and mode of administrations are contemplated and are encompassed as well as wide range of situations, wherein the prevention of chronic allograft rejection encompasses human patients who are allograft recipients of unspecified organs or body parts as claimed. The results desired appear to be highly dependent on all variables, the relationship of which is not clearly disclosed. Hence, one of ordinary skill in the art would not be able to show or demonstrate the enablement for a method for prevention of chronic allograft rejections in a patient by administering a combination comprising CSA with 2-CDA as recited in claims 13-24. Thus, Applicant has not established any *nexus* between all kinds of dosages and mode of administrations and their use in the manner claimed.

Further, the first paragraph of 35 U.S.C. 112 requires, *inter alia*, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). While patent Applicants are not directed to disclose every species that falls within a generic claim, id. At 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Where practice of the full scope of the claims would require experimentation; factors to be considered in determining whether a disclosure would require undue experimentation ..... include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Therefore, in view of the above, and in view of the fact that there is no enablement in the instant specification for all kinds of dosages and mode of administrations as well as preventing chronic allograft rejection in an allograft recipient in the manner claimed in the claims of the instant invention. Thus, applying the *Wands* factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of prevention for the reasons given above. Therefore, the specification does not enable any person skilled in the art to which it pertains, or which is most nearly connected, to use the invention commensurate in scope with the claims. In the express absence of one or more examples, evidence and sufficient guidance, the skilled artisan would be faced with undue experimentation for practicing the invention.

CONCLUSION AND FUTURE CORRESPONDANCE

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, CAMPELL BRUCE can be reached on (571) 272 0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JON WEBER
SUPERVISORY PATENT EXAMINER

/Mohamed/AAM
January 19, 2006